REMARKS/ARGUMENTS

In response to the Final Rejection mailed January 30, 2004, Applicants have amended claims 85, 88, 98 and 101, added new claims 106-111 and present the following remarks. Claims 85-94, 96 and 97-111 are pending. Claims 1-84, and 95 have been canceled.

Claims 85, 88, 98 and 101 were amended to avoid obvious typographical errors. Claim 98 has also been amended to overcome a rejection. Claims 106-111 were added to encompass measurement of polypeptide fragments specifically as the present invention does not require measuring the complete whole protein. For example, a polypeptide fragment may be measured such as those resulting from trypsin digestion and detected by mass spectrometry and exemplified in specification example 2.

The examiner has objected to the specification for a lack of definition of the terms "abundance" and "derivatization status" when describing a protein at a particular location in the specification. These terms do not require a separate definition, as they are understood in the art. Furthermore, the meaning of the terms is further elaborated on at several locations in the specification itself including a location two paragraphs later.

Claims 88 and 101 were objected to as containing a grammatical error. They typographical error is corrected above.

Claims 85-94 and 96-105 are rejected to because the following terms are not defined in the specification: "a degree of efficacy", a degree of effective response", "effective response", "relative amount of toxicity or effectiveness", "effective amount", and "greater than effective amount". This rejection is respectfully traversed.

It will be appreciated that all compounds are toxic to biological systems at some amount. The recognition of toxicity is also a well-understood concept. Likewise, well-established effective drugs (or other bio-effecting agents) are only effective when used in sufficient amounts. It will be appreciated that certain low

amounts of toxicity may be acceptable and certain low amounts of efficacy are NOT acceptable. All claims involve comparing the marker(s) (or fragments) in a test sample to the same in a control sample or other sample exposed to a known toxic or a known effective agent. Within this context, the objected to terms are appropriately used.

Claim 88 was considered confusing because of alleged unclearness of what "levels" refer to. In Claim 88 levels refers to levels of protein markers. Claim 88 has been amended. Also note the definition in the specification on page 8.

Claims 97, 104 and 105 were considered indefinite by reciting "the greater amount: and "an amount greater than". In claim 97, the term refers to that in claim 96. In claims 104 and 105, the terms are relative to the "effective amount of the antilipemic agent" as described in the parent claim.

Claim 98 was noted to lack antecedent basis for "the" abundance. This claim has been amended to overcome the rejection.

Claims 85-94 and 96-105 were rejected under 35 USC 112, first paragraph, for lack of enablement. The examiner specifically notes that the specification fails to describe a degree of toxicity and/or efficacy and its measurements. Rather the examiner urges only a change in the ratio or levels of marker proteins have been shown. However, as shown in the specification, the experiments involved the use of toxic and efficacious dosages of various agents and the change in protein marker abundances was measured. Therefore, the functional toxicity or efficacy is already present and the change in marker protein abundances from one group to another group or control represents a previously recognized change in efficacy or toxicity. Accordingly, it is proper to state that the demonstrated changes in the examples do correlate with differences in toxicity or efficacy.

The examiner also asserts that the method has not been shown to be quantitative and that no calibration curve has been shown. The specification shows data where three amounts of agent were used (control/zero dose, low/effective dose and high/toxicity dose). A calibration curve can be drawn between three points. More importantly, quantitative measurements were taken and one has the values

for control, effective and toxic reactions for certain particular protein markers. Quantitative measurements were taken for the same protein marker with several different drugs also which can easily be compared by viewing the Tables in the specification. Therefore, the results are quantitative.

Interestingly, the examiner mentions a lack of showing a relationship between the claimed markers and blood transaminases. Blood transaminases are traditional markers for liver toxicity but they are qualitative. The examiner has not established that blood transaminases levels can determine the **relative** toxicity of a drug. Thus, applicants have shown a superior toxicity measurement than that which the examiner contends to be enabled.

Still further, the rejection cites applicants' previous publications as prior art. The present specification is more detailed and more extensive than either or both of these previous publications. It is inconsistent and illogical to contend that such publications can be enabling prior art while still considering the more detailed specification to lack enablement. Accordingly, the rejection for grounds of lack of enablement should be withdrawn.

Claims 93, 94, 96-99 and 103-105 were rejected under 35 USC 112, first paragraph, for lack of enablement. The rejection states that the specification does not teach "pharmaceutically appropriate", "effective", "greater than effective" and "toxic" amounts or dosages. This rejection is traversed.

Several of the agents used in the specification are conventional FDA approved pharmaceuticals. These pharmaceuticals have well-established effective dosages, which should provide much guidance as to the dosages questioned by the examiner. Furthermore, among other the locations in the specification, Example 1, first paragraph, provides the exact amount of lovastatin provided to each group of rats. Therefore, the specification provides sufficient guidance for enablement of such descriptors and the rejection should be withdrawn.

Claims 85-94 and 96-105 were rejected under 35 USC 102(b) as being anticipated by Anderson et al (1991) and Anderson et al (1995). The examiner contends that Anderson et al (1991) exposed rats to a drug and measured the

abundances of various proteins as compared to controls and that some of the proteins showing altered abundance are the same as those listed in the claims. This rejection is respectfully traversed.

The examiner has confused the two Anderson et al references. Anderson et al 1991 merely lists proteins found in rat livers. Only a few, such as MSN 413 HMG Co-A synthetase, were changed in abundance due to any drug treatment. These few are NOT listed in the present claims.

The list in Anderson et al 1991 Addendum 2: Tables 1-4 is a master list of proteins in the rat liver database. This is not a list of protein markers. This table is for all spots as stated on page 911, first column, lines 15-19, "The gel X-coordinates of all liver protein spots...(Table 1)..." and page 910, second column, last paragraph, "...are listed for each spot (Table 1)."

Anderson et al 1994 recites several proteins that appear to be protein markers for exposure to a pharmaceutical. However, none of these proteins is listed in the present claims above. Whether Anderson et al (either) discloses other protein markers for drug effects does not suggest that additional other markers exist and cannot suggest using the specific markers listed in the claims.

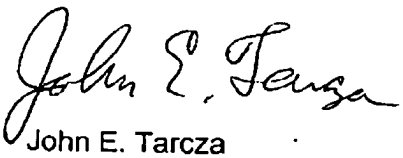
As a separate issue, neither Anderson et al reference discloses using an amount much greater than the effective amount and neither discloses using a toxic amount of the drug or treatment as claimed in the dependant claims. Furthermore, the previous Anderson references are comparing only single proteins, not patterns of plural proteins.

Therefore, neither Anderson et al reference teaches that the specifically claimed protein markers (or fragments thereof) are useful for determining toxicity or efficacy of an agent.

In view of the above amendments and comments, the claims are now in condition for allowance and applicants request a timely Notice of Allowance be issued in this application. If needed applicants petition for sufficient extension of time for consideration of this paper.

The commissioner hereby is authorized to charge payment of any fees, including extension of time fees, under 37 CFR § 1.17, which may become due in connection with the instant application or credit any overpayment to Deposit Account No.500933.

Respectfully submitted,



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